

**REMARKS/ARGUMENTS**

All claim amendments are made without prejudice and do not represent an acquiescence in any ground of rejection. Reconsideration of the captioned application based on the previous amendments and following remarks is respectfully requested.

**STATUS OF THE CLAIMS**

Claims 1-12, 14, 20, and 21 are under examination. After entry of this amendment, claims 1-9, 20 - 23 will be pending and under consideration.

Claims 1, 20, and 21 have been amended to more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants submit that the amendments are fully supported by the specification as filed, and no new matter is being added. The term "AZT susceptibility" has a well understood meaning in the art, and has been used through out the application as originally filed.

The amendments canceling claims 10 – 12, and 14 are being made solely to advance the prosecution of the instant application and are not in any way to be construed as an admission that the canceled material is unpatentable. Thus, Applicants reserve the right to pursue coverage of the canceled material by filing a continuation or a divisional application at an appropriate time in the future.

Applicants further submit new Claims 22 and 23, which are being added to present claims of varying scope. Support for new Claim 22 is found through out the application as originally filed, for example, on page 24, line 16 of the specification. Support for new Claim 23 can be found, for example, from Example 3 as originally filed.

**REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH**

Claims 1-12, 14, 20, and 21 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants have amended the claims for greater clarity and consistency of claim language. Those skilled in the art would understand the scope of the claims as amended when the claims are read in light of the specification. Applicants submit that the claims as amended are definite and particularly

point out and distinctly claim the subject matter which the Applicants regard as their invention. Thus, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC §112, second paragraph.

### **REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH**

Claims 1-12, 14, 20, and 21 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have amended the claims.

As the Examiner pointed out in the Office Action (dated May 16, 2005), the disclosure states that the invention is directed toward methods for identifying HIV-1 RT-resistance. For example, in Example 1, as originally filed from page 19 line 1 to page 28 line 7, the application particularly teaches a method for determining AZT susceptibility of a HIV-1 RT enzyme. Claim 1 has now been amended to cover such a method.

Also as the Examiner observed that the invention provides methods for identifying specific mutations or combinations of mutations involved in HIV resistance. For example, as originally filed in Example 2, from line 9 page 28 to line 16 page 31, the application particularly teaches a method for identifying at least one mutation in an HIV RT enzyme that increases or decreases the AZT susceptibility of the HIV RT enzyme. Claim 20 has now been amended to cover such a method. Claim 21 has now been amended to cover a method for rapid screening of mutations in a HIV RT enzyme that increases or decreases the AZT susceptibility of the HIV RT enzyme. Written description support for the amended claim 21 can be found from the originally filed application, for example, from Example 2, page 13 line 5 to 14, page 14 line 3 to 12, and the originally filed claim 21, etc.

Applicants submit that the claims as amended have written description support throughout the originally filed application. One skilled in the relevant art would have

reasonably believed that the inventor(s), at the time the application was filed, had possession of the claimed invention. Thus, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC §112, first paragraph.

#### **NEWLY IDENTIFIED PRIOR ART**

In the Office Action (dated May 16, 2005), the Examiner considered additional prior art to be allegedly germane to Applicant's disclosure: the Shafer paper (1998, *Ann. Intern. Med.* 128(11): 906-11) and the Winters paper (1998, *J. Clin. Invest.* 102(10): 1769-1775).

The Shafer paper describes "Multiple concurrent reverse transcriptase and protease mutations and multidrug resistance of HIV-1 isolates from heavily treated patients." The paper provides no description or teaching on in vitro enzymatic assay methods for determining the AZT susceptibility of a HIV RT enzyme. Instead, it describes a viral phenotypic assay for drug susceptibility testing. The present application, as currently amended, claims in vitro enzymatic assay methods of determining the AZT susceptibility of a HIV RT enzyme. The Shafer paper neither anticipates the current claims nor renders the current claims obvious. Applicant(s) fails to see the paper to be germane to the present invention, and respectfully traverse such a conclusion from the Examiner.

The Winters paper describes "A 6-basepair insert in the reverse transcriptase gene of human immunodeficiency virus type 1 confers resistance to multiple nucleotide inhibitors." The paper discloses a virion-associated RT inhibition assay using a commercially available RT assay kit from NEN Life Science (Boston, MA). This assay is distinct from the current invention in several aspects. For example, the RT assay kit from NEN Life Science did not contain the at least one ribonucleotide chosen from ATP or GTP, or at least one pyrophosphate as a reaction component. In addition, the Winters paper presents no data or evidence suggesting that the virion-associated RT inhibition assay had been successful in determining AZT susceptibility of a HIV RT enzyme. The present invention successfully detected AZT susceptibility of a HIV RT

enzyme using in vitro enzymatic assay methods that included at least one ribonucleotide chosen from ATP or GTP, or at least one pyrophosphate as a reaction component. Applicants urge that the teaching of the Winters paper neither anticipates the present invention nor renders the present invention obvious. Applicants respectfully traverse the Examiner's conclusion that the Winters paper is germane to the present invention.

### **REJECTIONS UNDER 35 U.S.C. §103(a)**

The Examiner has previously rejected claims from the present invention under 35 U.S.C. §103(a), see Office Actions dated January 10, 2002, August 22, 2002, March 23, 2003, November 30, 2003, and August 22, 2004. In anticipation of a reiteration of these rejections by the Examiner, below Applicants present responses to the combinations of references cited previously.

Obviousness under 35 U.S.C. §103(a) is a question of law based on the following factual inquiries: 1) the scope and the content of the prior art; 2) the differences between the prior art and the claims at issue; 3) the level of ordinary skill in the art; and 4) objective evidence of secondary considerations. Graham v. John Deere Co., 383 U.S. 1, 17, 148 U.S.P.Q. 459, 567 (1966).

The fact that a patent specifically discloses and claims a combination of features previously used in two separate devices (or methods) is not fatal to patentability. A basic issue is whether applied references, alone or in any combination, suggest the claimed invention as a solution to the specific problem solved. The claimed invention achieved new and unexpected results nowhere suggested in the prior art, and that achievement was overlooked. It is erroneous to focus the inquiry "solely on the product [or methods] created, rather than on the obviousness or non-obviousness of its creation." The initial inquiry should be directed to the vintage point of attacking the problem solved by the invention at the time the invention was made. When prior art itself does not suggest or render obvious the claimed solution to that problem, the art involved does not satisfy the

criteria of 35 U.S.C. §103(a) for precluding patentability. Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452 (Fed. Cir. 1984).

1. Meyer et al (1999) in view of Ekstrand et al (1996) does not render the present invention obvious.

Meyer et al. (1999) describes that "HIV-1 RT containing the D67N, K70R, T215F, and K219Q amino acid substitutions (designated as 67/70/215/219 RT in this report) was much more efficient than WT RT at extending the primer past several potential termination sites in the presence of AZTTP when ATP was added to the reaction." Ekstrand et al (1996) provides a non-radioactive RT assay that employs BrdUTP as the detectable dNTP.

Applicants discovered, for the first time, that adding at least one ribonucleotide chosen from ATP or GTP, or adding at least one pyrophosphate to an in vitro HIV RT enzymatic assay involving a detectable dNTP substrate, such as the non-radioactive assay of Ekstrand et al. (1996), not only enabled in vitro detection of AZT resistance for the mutant HIV RT enzymes in general, but also yielded much sensitive detection of AZT resistance than Meyer et al. (1999).

Meyer et al. (1999) is distinct from the present invention in at least that Meyer et al. did not employ a detectable dNTP substrate in their HIV RT assay, while methods of the present invention include a detectable dNTP substrate as a claim element. Ekstrand et al. (1996) is distinct from the present invention in at least that the non-radioactive RT assay of Ekstrand et al. did not contain the at least one ribonucleotide chosen from ATP or GTP, or at least one pyrophosphate as a reaction component.

Meyer et al. (1999) in view of Ekstrand et al (1996) does not render the present invention obvious under 35 U.S.C. §103(a). Applicant discovered that adding at least one ribonucleotide chosen from ATP or GTP, or adding at least one pyrophosphate to an in vitro HIV RT enzymatic assay involving a detectable dNTP substrate achieved new and unexpected results over what would be predicted by merely combining Meyer et al.

(1999) with Ekstrand et al (1996). The new and unexpected results were nowhere suggested in Meyer et al. (1999) or Ekstrand et al (1996). And, that achievement was overlooked during the past office actions.

Methods of the present invention are much more sensitive in detecting AZT resistance in vitro than the enzymatic assays Meyer et al. (1999) described. Meyer et al. assayed AZT resistance of the 67/70/215/219 mutant RT in vitro. The mutant had about 98-fold increase in AZT resistance when measured from a viral phenotypic assay (Larder and Kemp, 1989, *Science* 246:1155–1158, Table 2). However, only about 5-fold increase in AZT resistance was detected when Meyer et al. analyzed the mutant in vitro in the presence of 3.2 mM ATP (Meyer et al., Table 1). In comparison, Applicants measured AZT resistance of a wide range of mutant HIV RTs in vitro. These HIV RT mutants had increased AZT resistance ranging from about 2-fold to about 26-fold when measured from a viral phenotypic assay (Table 3, page 29 of the application as originally filed). Applicants discovered that, with most of the mutants tested, in the presence of 3.2 mM ATP, a method of the present invention detected AZT resistance in vitro similar to or within a factor of 2 of the resistance measured from the viral phenotypic assay (Table 3, page 29 of the application as originally filed).

At most, the teaching in Meyer et al. (1999) might make it obvious for a skilled artisan to try to add ATP to the non-radioactive assay of Ekstrand et al. (1996). However, obvious to try is an improper basis for a § 103(a) rejection when there is no suggestion or expressed expectation of success in the prior art that would have led one to perform the experimentation in the first place. Although obviousness does not require absolute predictability, a reasonable expectation of success is necessary. In re TomlinsonHall and Geigle, 363 F.2d 928 (C.C.P.A. 1966); In re Clinton, 527 F.2d 1226 (C.C.P.A. 1976).

Applicant(s) urges that in the instant case, there was no reasonable expectation of success that adding ATP to the non-radioactive assay of Ekstrand et al. would yield significantly better detection of AZT resistance than Meyer et al. (1999). Although Ekstrand et al. described the non-radioactive assay as "simple, sensitive and non-

radioactive", they did not directly compare the non-radioactive assay with the assay used by Meyer et al. Even if we assume, arguendo, the non-radioactive assay is more sensitive in measuring RT activity than that which was used by Meyers et al., the non-radioactive assay would have detected increased RT activity from both the WT RT enzyme and the mutant RT enzyme. It is unexpected that adding ATP to the non-radioactive assay would result in significant better detection of AZT resistance than adding ATP to the assay used by Meyers et al. Only by actually adding ATP, GTP, or PPi to the non-radioactive assay of Ekstrand et al. and carrying out the requisite steps, Applicants have discovered the unexpected result of better detection of AZT resistance in vitro than Meyer et al. Hence, it may be obvious to try, but such is not the standard under which obviousness established because a reasonable expectation of success is not present in this case.

In addition, Meyer et al. (1999) tested only the 67/70/215/219 mutant RT enzyme. Given the unpredictability of the HIV AZT resistance at the time of the invention, one questioned whether the enhancement effect of ATP on the detection of AZT resistance Meyer et al. observed in their RT enzymatic assay was specific to the one particular mutant they tested or equally applicable to other HIV mutants in general. With much effort and persistence, Applicants cloned, isolated, and tested a wide range of mutant HIV RT enzymes to finally establish a convincing correlation between the enhanced detection of AZT resistance and the presence of at least one ribonucleotide chosen from ATP or GTP, or at least one pyrophosphate in the assay. Methods of the present invention provide a solution to the specific problem of correlating results from an in vitro enzymatic assay with those from a viral phenotypic assay for a wide range of mutant HIV RT enzymes. Such a solution is neither described nor suggested by Meyer et al (1999) or Ekstrand et al (1996). "It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to [use] that which the inventor taught against its teacher." (Quoting W.L. Gore v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983)). In re Lee, 61 U.S.P.Q.2d at 1434 (Fed. Cir. 2002). The Examiner took "the inventor's disclosure as a blueprint for piecing together the prior

art to defeat patentability – the essence of hindsight.” In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999).

Indeed, Meyer et al. published their work about three years after Ekstrand et al (1996), but chose to add ATP to an assay different from that of Ekstrand et al. This fact alone suggests that it was not obvious, as Examiner suggested with hindsight, to add ATP to the non-radioactive assay of Ekstrand et al. (1996) for increased detection of AZT resistance. Indeed, had Meyer et al. expected better detection of AZT resistance by adding ATP to the non-radioactive assay of Ekstrand et al., Meyer et al. would likely have chosen to add ATP to the non-radioactive assay of Ekstrand et al. instead, or at least had suggested the combination of ATP and the non-radioactive assay of Ekstrand et al. in their paper. Inability of an expert to predict the results obtainable with a claimed product suggests non-obviousness, not routine experimentation. Uniroyal Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044 (Fed Cir. 1988).

For the reasons detailed above, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC § 103(a) over Meyer et al (1999) in view of Ekstrand et al (1996).

2. Arion et al (1998) in view of Ekstrand et al (1996) does not render the present invention obvious.

Arion et al. (1998) also only tested the AZT resistance of the mutant HIV-1 RT containing the D67N, K70R, T215F, and K219Q amino acid substitutions, and found that the presence of physiological concentrations PPi (150  $\mu$ M) resulted in increased detection of AZT resistance in vitro.

Arion et al. (1998) is distinct from the present invention in at least that Arion et al. did not employ a detectable dNTP substrate in their HIV RT assay, while methods of the present invention include a detectable dNTP substrate as a claim element.

Arion et al. (1998) in view of Ekstrand et al (1996) does not render the present invention obvious under 35 U.S.C. §103(a). Arguments similar to those presented supra related to Meyer et al (1999) in view of Ekstrand et al (1996) apply here. In addition, because the result of Arion et al (1998) was later contradicted by Meyer et al. (1999), a

skilled artisan in the relevant art would be even less motivated to combine Arion et al. (1998) with Ekstrand et al (1996), and would have even less reasonable expectation of success from the combination.

For the reasons detailed above, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC § 103(a) over Arion et al (1998) in view of Ekstrand et al (1996).

3. Meyer et al. (1999) in view of Ueno et al. (1995) does not render the present invention obvious

Ueno et al (1995) describe an in vitro HIV RT assay that employs radioactive labeled dNTPs. Ueno et al. (1996) is distinct from the present invention in at least that the RT assay of Ueno et al. did not contain the at least one ribonucleotide chosen from ATP or GTP, or at least one pyrophosphate as a reaction component.

Arguments similar to those presented supra related to Meyer et al (1999) in view of Ekstrand et al (1996) apply here.

For the reasons detailed above, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC § 103(a) over Meyer et al (1999) in view of Ueno et al (1995).

4. Arion et al. (1998) in view of Ueno et al. (1995) does not render the present invention obvious

Arguments presented supra related to Meyer et al (1999) in view of Ueno et al (1995), and Arion et al. (1998) in view of Ekstrand et al (1996), apply equally here.

For the reasons detailed above, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC § 103(a) over Arion et al (1998) in view of Ueno et al (1995).

## CONCLUSION

Entry of the foregoing amendment is respectfully requested because the amendment is believed to place the application in condition for allowance or, in the alternative, in better condition for appeal.

Applicants respectfully request that the Examiner withdraw the rejection under 35 USC §112, second paragraph, because Applicants submit that the claims as amended are definite and particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. Applicants respectfully request that the Examiner withdraw the rejection under 35 USC §112, first paragraph, because Applicants submit that the claims as amended have written description support throughout the originally filed application, and that one skilled in the relevant art would have reasonably believed that Applicants, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the Examiner's conclusion that the Shafer paper (1998, *Ann. Intern. Med.* 128(11): 906-11) and the Winters paper (1998, *J. Clin. Invest.* 102(10): 1769-1775) paper is germane to the present invention, because Applicants urge that the teaching of the papers neither anticipates the present invention nor renders the present invention obvious. Applicants respectfully request that the Examiner withdraw the rejection under 35 USC § 103(a) over Meyer et al (1999) in view of Ekstrand et al (1996), Arion et al (1998) in view of Ekstrand et al (1996), Meyer et al. (1999) in view of Ueno et al. (1995), Arion et al. (1998) in view of Ueno et al. (1995), etc., because methods of the present invention achieved new and unexpected results over what would be predicted by merely combining the references, and that methods of the present invention provide a solution to the specific problem of correlating results from an in vitro enzymatic assay with those from a viral phenotypic assay for a wide range of mutant HIV RT enzymes.

In view of the foregoing amendments and remarks, Applicants submit that the application is in condition for allowance, and respectfully request that a timely Notice of Allowance be issued in this case.

Should the Examiner have any questions or concerns regarding the present response, he/she is invited to contact the undersigned at the telephone number provided below.

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